IN THE DRAWINGS

No amendment

REMARKS

This paper replaces the Amendment filed 22 March 2006. This paper being timely submitted, no fee is believed due.

Anticipation

All claims stand rejected as anticipated by Sven PALMÉR *et al., Manufacturing Process of Metoprolol*, United States Letters Patent No. 6,252,113 (26 June 2001) or by Josep M. RIBALTA BARO *et al., Industrial Process For Obtaining An Aryloxypropanolamine*, United States Letters Patent No. 5,082,969 (21 Jan. 1992). Reconsideration is respectfully requested.

The OFFICE ACTION alleges that claim 1 of the instant application "broadly reads on" RIBALTA BARO's Examples 1-2 and on PALMÉR's Working Example. Whether or not the claim "broadly reads on" a reference, however, is not the applicable legal standard.

Rather, the claim is anticipated if - and only if – "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir., 1987); *see also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir., 1989) (the prior art must teach the invention in as complete detail as is contained in the claim).

In the immediate case, claim 1 enumerates six distinct claim elements. In contrast, the OFFICE ACTION fails to allege the presence of each of these elements in either reference. This is not surprising because neither reference in fact teaches every claim element. For example, the OFFICE ACTION correctly fails to allege that RIBALTA BARO's Examples 1-2 teaches claim elements A), C), D) and I). Similarly, the OFFICE ACTION correctly fails to allege that PALMÉR's Working Example teaches claim elements C), D), E), F) and I).

Further, the prior art must teach each claim element in the arrangement required by the claim. *In re Bond*, 910 F.2d 831 (Fed. Cir., 1990). In the instant case, claim 1 requires reacting a phenol and epichlorhydrin in an alkaline medium:

A) combining 4-(2-methoxyethyl)phenol with epichlorhydrin;

B) reacting said combination of 4-(2-methoxyethyl)phenol and epichlorhydrin in an alkaline aqueous medium;

In contrast, RIBALTA BARO's Examples 1-2 teach reacting a phenol with a sodium-ion donor to make sodium phenolate, and then reacting that sodium phenolate with epichlorhydrin:

A) combining 4-(2-methoxyethyl)phenol with an aqueous sodium-ion containing medium to make sodium phenolate, *see* col. 2, lines 46-48;

B) reacting said sodium phenolate with epichlorhydrin, *see* col. 2, lines 48-50;

RIBALTA BARO's Examples 1-2 cannot anticipate as a matter of law because it fails to teach the same arrangement required by claim 1. *See In re Bond*, *supra*.

Withdraw of the anticipation rejections is respectfully believed necessary because the OFFICE ACTION fails to state a *prima facie* case of anticipation.

Obviousness

All claims stand rejected as obvious in light of PALMÉR *combined with* RIBALTA BARO. Reconsideration is respectfully requested.

The OFFICE ACTION alleges that claim 1 of the instant application is "substantially disclosed" in RIBALTA BARO's Examples 1-2 and PALMÉR's Working Example. Whether or not the claim is "substantially disclosed" by the art of record reference, however, is not the applicable legal standard.

Rather, to establish a *prima facie* case of obviousness, all words in a claim must be considered. *See In re Wilson*, 424 F.2d 1382, 1385 (C.C.P.A., 1970). Thus, the combined prior art must teach each and every claim limitation. *See In re Royka*, 490 F.2d 981 (C.C.P.A., 1974).

In the instant case, claim 1 enumerates six distinct claim elements. In contrast, the OFFICE ACTION fails to allege the presence of any of these elements in the combined references.

This is not surprising because the combined references do not teach every claim element. For example, the combined references fail to teach claim elements C), D) and I). Rather, the OFFICE ACTION recognizes that the pH claimed in element C) is "not explicitly disclosed in the examples of the prior art." The OFFICE ACTION fails to state a *prima facie* case because the OFFICE ACTION fails to allege where each and every claim element is taught in the art of record.

Furthermore, even if the prior art teaches the genus, a specific species may be patentable where that species shows unexpected synergy over the disclosed genus. For example, where the prior art teaches that a reaction with "an alkaline chlorine or bromine solution" such as sodium hypobromite will yield 35.4%, achieving an unexpectedly-high yield of 64.3% using sodium hypochlorite is patentable. *In re Meyer*, 599 F.2d 1026 (C.C.P.A., 1979).

Similarly, even if the prior art teaches to use sulfuric acid, a specific concentration of sulfuric acid species may be patentable where that species is critical for the success of the claimed invention. For example, where the prior art teaches that a reaction uses "concentrated sulfuric acid," achieving an

unexpectedly-high purity using a specific concentration (98%) of sulfuric acid is patentable. *Akzo N.V. v. United States International Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir., 1979).

In the instant case, assuming the prior art teaches the genus of solutions with a pH, the inventors allege that they have achieved an unexpectedly-high yield using a solution with the claimed specific pH. This specific pH range therefore appears non-obvious. *See In re Meyer; Akzo v. U.S.*

As support for an obviousness rejection, the OFFICE ACTION relies on *In re Aller*, 220 F.2d 454 (C.C.P.A., 1955). Reconsideration is respectfully requested.

In *Aller*, the prior art of record disclosed the same parameters (temperature and sulfuric acid concentrations) claimed by the applicant. *See id.* at 455. In contrast, in the instant case, the claims recite a specific pH range, while the art of record fails to mention any pH range at all.

Further, the prior art in *Aller* itself suggested the desirability of modifying the prior art ranges. *See Ex parte Sullivan, Patent Application Serial No. 09/110,221*, (B.P.A.I., 2003), *citing In re Aller*. In the instant case, the OFFICE ACTION does not allege that the art of record mentions pH at all, nor that the prior art suggests modifying any prior art pH range. Thus, *In re Aller* is not controlling.

Further, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation, the prior art must teach that the particular parameter at issue is "result-effective," *i.e.,* a variable which achieves a recognized result. For example, in *In re Antonie*, 559 F.2d 618 (C.C.P.A., 1977), the claims covered a water treatment device with a tank volume : contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume : contractor ratio. The Circuit Court of Patent Appeals (the predecessor to today's Federal Circuit) held that because that ratio was not recognized in the prior art as a "result-effective" variable, optimizing it is *not* routine.

In the instant case, the OFFICE ACTION fails to allege that the prior art teaches any particular pH of the reaction mixture *at all*, much less teach that pH is a "result effective" variable. Thus, the art of record fails to suggest modifying that variable in the claimed manner.

Because the OFFICE ACTION fails to allege that the art of record teaches each element of the claims, and because the art of record fails to fairly suggest modifying the prior art in the claimed manner, the OFFICE ACTION fails to state a *prima facie* case of obviousness.

The Specification

The Examiner argues that pages 2-4 of the Specification provide a basis to invalidate the immediate claims. Reconsideration is respectfully requested because pages 2 to 4 of the Specification explain how the claimed invention is patentably distinct from the art of record. Specifically, while the claimed *raw materials* are known in the art, the Inventors have found that the claimed *solvent system*, the claimed *pH of the wash,* and the claimed *reaction temperature* are not taught in the prior art. Furthermore, the Inventors have found that these factors crucial to success of the claimed invention because the claimed reaction conditions provide surprisingly synergistic results.

The Specification at pages 2 to 4 says, in relevant part:

> Reactions which are carried out at lower temperatures (below ambient room-temperature) leads to a relatively slow rate of reaction; in contrast, more impurity levels occur when the reaction is carried out at higher temperature range, so that while the rate of reaction is increased, the resulting product requires purification by distillation under a high vacuum.
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> In the processes where purification of the epoxide is avoided, the resultant products are formed with higher impurities. The processes involving excess use of isopropyl amine leads to increased costs. The products formed with higher impurity levels necessitate extra purifications, which increases the cost of manufacturing the product.
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> * * *
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> The present invention has made it possible to produce metoprolol base and its salts in higher yields, and with high purity,

and avoiding processes like high-vacuum distillation, thus enabling cheaper manufacturing costs.

The present invention involves optimization of reaction temperatures and the molar ratio of reactants in order to achieve higher-purity and higher yields, by avoiding the excessive manufacture of epoxide intermediates seen in the prior art teachings, and thus avoiding the need for purification of these epoxide intermediates.

The present invention process involves three steps. The first step is for preparation of epoxide by reacting 4-(2-methoxyethyl) phenol with epichlorohydrin in an aqueous media containing inorganic base such as sodium hydroxide at 40-45°C temperature, rather than the lower temperature range taught by [RIBALTA BARO] nor the higher temperature range taught by [PALMÉR].

As with the prior art teachings, at the end of the reaction, the aqueous and organic phases are separated out. In contrast to the prior art teachings, however, in our process the organic phase is washed thrice by water, and we have found that the pH of the washing water must be in the range of pH 7 to 8; this pH range is necessary to achieve high purity of the epoxide.

The resultant epoxide is used in the second step for preparation of metoprolol base. The epoxide is treated with isoproplyamine in aqueous media to obtain Metoprolol base of high purity in high yields. The last step is converting metoprolol base into the succinate and tartrate salts, by reacting the metoprolol base with an acid (such as succinic acid or tartaric acid) in solvent media (such as acetone) by any conventional method. This last step - reacting in an organic solvent such as acetone, rather than in an aqueous media - contrasts with the teachings of the art, which discourage using organic solvents (*see e.g.*, [RIBALTA BARO] at column 2, lines 18-28 ("aqueous medium … present[s] notable advantages with respect to other processes which require organic solvents"); [PALMÉR] at col. 1, lines 37-44 ("The difference from the prior art is that the new method uses no other solvents than water for the reaction of A and B. From an environmental as well as an occupational hazard point of view it is a great advantage to be able to replace a hazardous organic solvent with

a non-noxious solvent such as water.")).

By following the present invention as described below, it has been made possible to produce metoprolol base and its salts in higher yields with high purity and avoiding processes like high vacuum distillation, at cheaper costs.

The present invention involves optimization of reaction temperatures, molar ratio of reactants in order to achieve higher purity and yields by avoiding purification of epoxide intermediates.

This explains how the claimed invention is patentably distinct from the art of record.

Summary

Applicant respectfully believes the claims are in condition for prompt allowance.

Respectfully Submitted on behalf of Applicant by its attorneys,
PHARMACEUTICAL PATENT ATTORNEYS, LLC

/s/
By Mark POHL, Reg. No. 35,325
55 Madison Avenue, 4th floor
Morristown, NJ 07960
(973) 984-0076

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